140. The process of claim 125 wherein when OD is imidoyl, the condensation reaction is carried out in a solvent in the presence of a catalyst at a temperature below or equal to $0^{o}C$.--

7 cont.

REMARKS

Favorable consideration of this Amendment is respectfully requested. This is a Supplemental Amendment to the Amendment under 37 CFR 1.111 and 1.115 filed December 29, 1986 in response to the Office Action mailed June 25, 1986.

The amendment to claim 101 corrects an inadvertant duplication of structures. The amendment to claim 104 corrects a typographical error. The amendment to claim 122 corrects an inadvertant typographical omission in the claim.

The newly presented claims 125-140 are process claims. These claims have been added to the application to more particularly point out and distinctly claim that which the applicants regard as their invention.

This invention relates to a process for the synthesis of heparinic mucopolysaccharide compounds and to the compounds which are synthesized as discussed in the prior Amendment. The ability to control the nature and position of the functional groups attached to the saccharides and the stereochemistry of the linkage between the saccharide units is crucial to a successful synthesis.

Applicants have discovered an unexpected sequence of steps which allows for the synthesis of the desired compounds. The sequence of the invention comprises 1) condensing the saccharide units to obtain the desired stereospecific linkage between the units; 2) removing select protecting groups to obtain free OH groups; 3) substituting these free OH groups with desired functional groups such as sulfates and phosphates and 4) removing the remaining hydroxy-protecting groups in the presence of the sulfate or phosphate groups to obtain free OH groups. Newly presented claim 125 is drawn to this sequence of steps.

The claimed sequence of steps is not taught or disclosed in the prior art.

In particular, the step of removing benzyl groups in the presence of sulfate groups is unexpected. The Examiner's attention is directed to the article of Turvey and Williams, J. Chem. Soc. 1962, 2119-2112. (Exhibit I, attached) where it is taught that the presence of sulfate groups interferes with the catalytic hydrogenation to remove benzyl groups. The article teaches that it required several repetitions of the hydrogenation to only partly remove the benzyl groups. (p. 2119, lines 16-19). The article further discloses that the authors then reverted to an alternate sythesis which accorded "a somewhat better yield" (Ibid, line 23). It is noted that even in the alternate synthesis, it was necessary to repeat the

hydrogenation 4 times in order to remove the benzyl groups. Thus, the successful removal of benzyl groups in the presence of sulfate groups of the instant invention is unexpected in view of the teaching of the prior art.

The sequence of steps as claimed also is not taught or suggested by the cited prior art. The references are silent with regard to the aspect of removing select protecting groups in the presence of other protecting groups.

The law "requires that an invention be considered as a whole" Carl Schenck A.G. v. Nortron Corp., 218 USPQ 698, (Fed. Cir. 1983). The Examiner has not considered the instant invention "as a whole" because it has not been shown that all of the claimed steps of the instant process are suggested by the cited prior art.

The law also requires that:

> ...there must have been something present in those teachings [of the prior art] to suggest to one skilled in the art that the claimed invention...would have been obvious, W.L. Gore and Associates, Inc., v. Garlock, Inc. 220 USPQ 303, 311 (Fed. Cir. 1983).

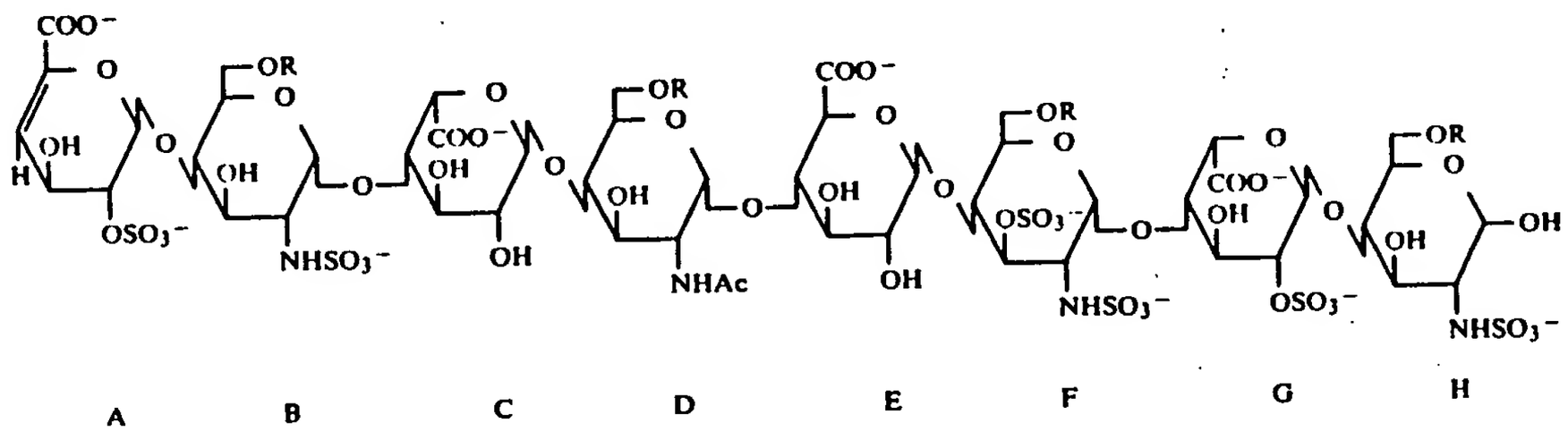
Here there is nothing in the teachings of the cited prior art to suggest the sequence of steps of the process of the invention as a whole.

In view of the above remarks it is submitted that the process claims are patentable over the cited prior art. Reconsideration is respectfully requested.

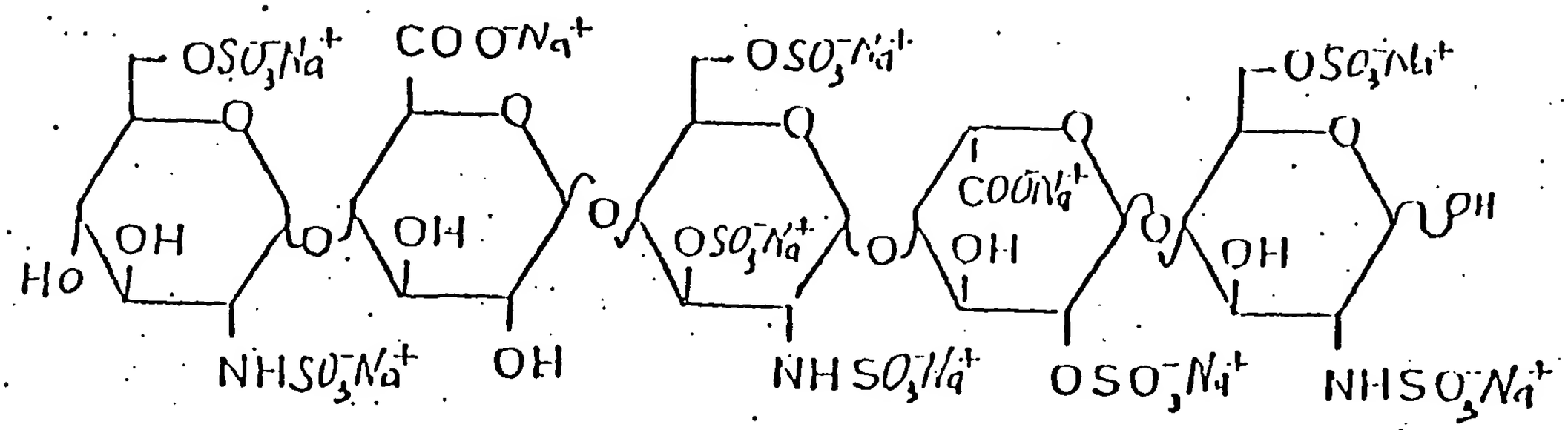
In the event that the Examiner remains unconvinced by the Remarks presented in the December 29, 1986 Amendment under 37 CFR 1.111 and 1.115 with respect to the rejection of claims 49-82 under 35 USC 102(a), (b), (e) and (f), and 35 USC 103, the Examiner's attention is directed to the fact that the subject matter of newly presented compound claims 89-96 and 98-105 are intermediate synthetic compounds. There is no suggestion, nor can there be any, in the cited patents of the synthesis of heparinic mucopolysaccharides since there is no synthetic route suggested. Accordingly there is no teaching or suggestion of the compounds, the claimed intermediates (claims 89-96, and 98-105).

With respect to the final compounds, there also is no teaching or suggestion of the compound of Claim 106.

If the Examiner, in rejecting the claim, is referring to the species DEFGH disclosed in the prior art, for example in '770, column 5, line 33, referring back to the main formula in columns 5 and 6



it will be noted that there are significant differences between DEFGH and the specific compound claimed



These differences are as follows.

It can be observed that there are 3 R substitutions in the 6 position of the glucosamine units of the prior art, wherein R can be hydrogen or sulfate. In the instant claimed compound all three R groups are sulfate. There is no teaching or suggestion in the cited patents to choose the particular arrangement of three sulfate groups from the eight possible combinations represented by the main formula.

More importantly, the substituent on the nitrogen of glucosamine D is fixed to be acetyl in the cited prior art. In the instant claimed compound the substituent is sulfate. There is no reason or suggestion in the prior art to replace the acetyl group with a sulfate group. It will be noted that the acetyl group is typical of natural heparin or fractions thereof ('770, col. 1, lines 40-42). In this therapeutic area, it has been desirable to simulate or mimic natural products.

Therefore, one skilled in the art would not be tempted to disrupt a natural occurring sequence to replace one group by any other group.

The compound claimed here is a synthetic compound (produced from the individual saccharide units) whereas the compounds of the prior art are obtained from the fractionation of naturally occurring heparin wherein the substituents on the saccharide rings are already in place. In addition to the differences with respect to the substitution at the 6-position of the saccharide ring, the compounds differ in the acetyl or sulfate substituent on the nitrogen.

Furthermore, if one were to think that these differences were merely structural changes, the changes are also reflected in the properties of the compound. Unexpectedly, it has a beneficial effect. This can be seen from a comparison of the reported anti-Xa activity for DEFGH of "over 400 u/mg" ('770, col. 18, line 40) with the anti-Xa activity "greater than 2000 u/mg", (page 46, line 6) of the compound of claim 106. Thus, there is a 50-fold increase in a valuable property, the antithrombotic property.

It is clear that compounds have to be taken together with their properties when determining unobviousness (In re Papesch, 137 USPQ 43 (CCPA 1963) and decisions following). Furthermore, the view of the court today with respect to

specific chemical structures which are alleged to be prima facie obvious one from the other is seen for example in In re Grabiak, 226 USPQ 870 (Fed. Cir., 1985). When discussing the substitution of sulfur for oxygen the Court states

> there must be adequate support in the prior art for the ester/thioester change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the client. In re Grabiak, 226 USPQ 870,872 (Fed. Cir., 1985).

Here the Examiner has not provided adequate support to perfect the PTO's prima facie case.

With respect to claim 97, it will be noted that the claim calls for the compounds to be synthetic and pure.

It is respectfully submitted that the instant claimed compounds are not obvious from the cited patents.

Additionally, the instant application has been amended to reflect its status as a continuation-in-part application of U.S. Applications Ser. Nos. 194,544 and 194,545. It is respectfully submitted that in view of the relationship of the cited patents and the instant application that the rejection of claims 49-82 under 35 USC 102 or, in the alterntive, under 35 USC 103 is now moot.

Should the Examiner believe that a telephone call to the undersigned or Gerard J. Weiser, attorney of record, would

favorably advance the prosecution of this application or narrow any outstanding issues, she is respectfully invited to call at the telephone number indicated below.

Respectfully submitted,

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Enclosures: Exhibit I

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 6, 1987

Elizabeth Jones
Signature

March 6, 1987
Date